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**The maternal immune response inhibits the success of in utero hematopoietic cell transplantation.**

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**Public Summary:**

With improvements in prenatal diagnosis and genetic testing, we can now diagnose a wide variety of congenital disorders that are amenable to stem cell based therapies. For example, many blood cell related and immunologic disorders can be potentially cured by stem transplantation. However, the current treatment of these disorders relies on postnatal bone marrow transplantation, which can carry significant morbidity. Treatment of these diseases in utero, prior to the maturation of the immune system, offers an innovative approach. With in utero stem cell transplantation, foreign cells transplanted before the immune system matures may be perceived as "self," thereby avoiding a host immune response. Clinically, however, this approach has only been successful in the setting of severe immunodeficiency. In this paper, we review our recent publication in which we utilized a mouse model of IUHCTx to confirm previously published findings that the adaptive immune system impairs foreign donor cell engraftment. Since the fetal immune system is relatively immature and cellular trafficking between a mother and her fetus is a well described phenomenon in human pregnancy, we hypothesized that maternal cells that travel into the fetus may pose the true barrier to donor cell engraftment. We demonstrated that there is a significant number of maternal immune cells in the blood of unmanipulated mouse fetuses, with significant increases in T cell trafficking after IUHCTx. Using genetically modified mice, we found that maternal T cells provided the main barrier to engraftment. In our experimental model, we also determined that genetically matching the donor cells to the mother resulted in high levels of engraftment. Our results indicate that suppressing the maternal immune system may be a useful approach to improve donor cell engraftment, and that the clinical success of IUHCTx may be improved by transplanting cells harvested from (or HLA-matched to) the mother.

**Scientific Abstract:**

In utero hematopoietic cell transplantation (IUHCTx) is a promising strategy for the treatment of congenital stem cell disorders. Despite the purported immaturity of the fetal immune system, the clinical success of this strategy has been limited by poor engraftment of transplanted cells. The fetal host immune system is thought to be the major barrier to achieving successful IUHCTx. Since the fetal immune system is immature, however, we hypothesized that the maternal immune response may instead pose the true barrier to IUHCTx. We have demonstrated that maternal T cells traffic into the fetus after allogeneic in utero transplantation and that these lymphocytes play a critical role in limiting engraftment. Furthermore, we have shown that MHC matching the donor cells to the mother improves engraftment in the unmatched fetus. These results help renew interest in using the fetal environment to treat patients with congenital stem cell disorders.

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